

REMARKS/ARGUMENTS

I. Status of the Claims

After entry of this amendment, claims 1-4, 9-10, 14-18, and 20-44 are pending. Claims 1, 14, and 15 have been amended. Claims 5-8, 11-13, 19, and 45-91 have been cancelled. The amendments contained herein do not introduce new matter or raise new issues that would require further consideration and/or search.

II. The Invention

The invention provides a new tool for the characterization of macromolecules in their natural environment. This characterization is achieved through the labeling of selected macromolecules in an intact biological compartment with a NMR-detectable nucleus such that the NMR-detectable nucleus is present in the selected macromolecule in an amount greater than is naturally abundant. Contacting the intact biological compartment with radio frequency energy, and then collecting and analyzing the data produced, provides structural, conformational and dynamic information for the labeled macromolecules contained within. For example, the methods of the present invention can distinguish individual macromolecules, macromolecule conformations, and interactions of macromolecules with other species within an intact biological compartment. In order to optimize the sensitivity of the NMR measurements of the invention, different expression and labeling schemes are used, such as employing the polymerase inhibitor rifampicin to lower background signals, and expressing the intact, living cells in label-rich media.

III. Support for the Amendments

Support for the amendments to the claims can be found throughout the specification, the drawings, and the claims as originally drafted.

Support for the amendments to claims 1, 14 and 15 are found on page 9, lines 30-34, as well as Examples 3 and 5-7.

IV. Response to Claim Rejections

Under 35 U.S.C. § 112, second paragraph, indefiniteness

a) Claim 91

Claim 91 is rejected for alleged vagueness and indefiniteness in the recitation in the preamble of "in an amount greater than is naturally abundant". Since claim 91 has been cancelled, Applicant respectfully requests withdrawal of the rejection.

Under 35 U.S.C. § 112, first paragraph, written description

a) Claim 90

Claim 90 is rejected for lack of written description for the phrase "the intact biological compartment is immobilized". Since claim 90 has been cancelled, Applicant respectfully requests withdrawal of the rejection.

Under 35 U.S.C. § 102

To maintain a *prima facie* case of anticipation, the Examiner must demonstrate that each and every element as set forth in the claim is either expressly found or is inherently described in a single enabling prior art reference. The identical invention must be shown in as complete detail as is contained in the ...claim. See MPEP § 2131. Applicant submits that one prior art reference of record (Williams) does not disclose each element of the claims now pending. In addition, Applicant submits that one prior art reference of record (Serber) cannot serve as a 35 U.S.C. § 102(a) prior art reference. Therefore, Applicant respectfully traverses these rejections.

a) Under 35 U.S.C. § 102(b): Over Williams

Claims 1-4, 10, 11, 14, 17, 18, 22, 23, 26, 29-32, 33, 34, 38, 41-44, and 90-91 are rejected as allegedly being anticipated under 35 U.S.C. § 102(b) by Williams, *et al.*, *BioPhysical Journal*, 72: 490-498 (1997) ("Williams"). Claims 11 and 90-91 have been cancelled. In the first Office Action response, Applicant differentiated the instant invention from Williams on two fronts. The first was Williams's inability to determine the macromolecular conformation information which was possible in Applicant's invention. The second was Williams's failure to

disclose the multidimensional NMR methods which are required in Applicant's invention. The Examiner noted that neither of these differentiating features are reflected in the rejected claims.

Therefore, Applicant amends claim 1 to include both of these differentiating features. Applicant amends claim 1 in order to define structural information as "a representation of a first conformation of said selected macromolecule at a resolution sufficient to determine the relative locations of two or more atoms". Support for this amendment is found in the specification on page 9, lines 30-32. Applicant also amends claim 1 in order to define the NMR data set as a "multidimensional" NMR data set. Support for this amendment is found in the specification in Examples 3 and 5-7.

Since Williams does not disclose a) the determination of the relative location of two or more atoms and b) the collection of a multidimensional NMR data set, Williams does not disclose each and every element of Applicant's invention. Accordingly, a *prima facie* case of anticipation can not be set forth. Therefore, claims 1-4, 10, 11, 14, 17, 18, 22, 23, 26, 29-32, 33, 34, 38, and 41-44 are in condition for allowance and Applicant respectfully requests withdrawal of the rejection.

b) Under 35 U.S.C. § 102(a): Over Serber

Claims 1-4, 10, 11, 14-17, 21, 29, 32, 38-42, and 89-91 are rejected as allegedly being anticipated under 35 U.S.C. § 102(a) by Serber, *et al.*, *J. Am. Chem. Soc.*, **123**: 2446-2447 (2001) ("Serber"). Claims 11 and 90-91 have been cancelled. In the first Office Action response, Applicant submitted an unsigned "Katz" declaration, with the promise of later submitting a signed declaration, in order to overcome any potential rejections over 35 U.S.C. § 102(a). In the second Office Action, the Examiner notes that the unsigned "Katz" declaration was never received. Therefore, Applicant respectfully submits a signed Katz declaration as Exhibit A for consideration in this case.

The Katz declaration establishes that Serber is a publication co-authored by the Applicant which describes Applicant's own work. Therefore, Serber is a disclosure by the Applicant of his own work within the year before the application filing date. Thus, Serber

cannot properly serve as a 35 U.S.C. § 102(a) reference. Applicant respectfully requests withdrawal of the rejection.

Under 35 U.S.C. § 103(a)

In order to establish a *prima facie* case of obviousness, the rejection must demonstrate that (1) the cited references teach all the claimed elements; (2) there is a suggestion or motivation in the prior art to modify or combine the reference teachings; and (3) there is a reasonable expectation of success. MPEP § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). As explained below, the cited references fail to disclose the determination of the relative locations of two or more atoms in a selected macromolecule in an intact biological compartment using multidimensional NMR methods.

a) Over Williams

Claims 27 and 28 are rejected as allegedly being obvious over Williams. Williams is described above. Applicant respectfully traverses.

As mentioned above, Applicant has amended claim 1 to differentiate the instant invention from Williams on two fronts. Since claims 27 and 28 are dependent from claim 1, they also contain these limitations. Since Williams does not disclose a) the determination of the relative location of two or more atoms in a macromolecule and b) the collection of a multidimensional NMR data set, Williams does not teach all of the claimed elements of Applicant's invention. Accordingly, a *prima facie* case of obviousness can not be set forth. Therefore, claims 27 and 28 are in condition for allowance and Applicant respectfully requests withdrawal of the rejection.

b) Over Williams, in view of Brown, et al. ("Brown"), and further in view of Fesik, et al. ("Fesik")

Claims 9, 20, and 35-37 are rejected as allegedly being obvious over Williams, in view of Brown (U.S. Patent No. 5,817,474), and further in view of Fesik (U.S. Patent No. 5,989,827). Williams is described above. Brown is cited for teaching a method for determining the three-dimensional structure conformation of a protein by growing a mammalian cell culture

which produces the protein in a nutrient medium which contains all the essential amino acids for the growth of cells, and wherein the amino acids are substantially isotopically labeled with NMR active isotope. Fesik is cited for teaching a method of identifying a small molecule ligand to the protein using two dimensional $^{15}\text{N}/^1\text{H}$ NMR correlation spectroscopy, then identifying a second small molecule ligand to the protein using two dimensional $^{15}\text{N}/^1\text{H}$ NMR correlation spectroscopy. Applicant respectfully traverses.

In the first Office Action response, Applicant differentiated the instant invention from the combination of Williams, Brown, and Fesik. The point of differentiation is that the combination does not teach or suggest the determination of the relative locations of two or more atoms in a selected macromolecule in an intact biological compartment through using multidimensional NMR methods. The Examiner noted that this differentiating feature is not reflected in the rejected claims.

Therefore, Applicant has amended claim 1 in order to define structural information as "a representation of a first conformation of said selected macromolecule at a resolution sufficient to determine the relative locations of two or more atoms". Support for this amendment is found in the specification on page 9, lines 30-32. Applicant has also amended claim 1 in order to define the NMR data set as a "multidimensional" NMR data set. Support for this amendment is found in the specification in Examples 3 and 5-7.

Since the combination of Williams, Brown, and Fesik does not disclose the determination of the relative locations of two or more atoms in a selected macromolecule in an intact biological compartment through using multidimensional NMR methods, the combination does not disclose each and every element of Applicant's invention. Accordingly, a *prima facie* case of obviousness can not be set forth. Therefore, claims 9, 20, and 35-37 are in condition for allowance and Applicant respectfully requests withdrawal of the rejection.

c) Over Williams, in view of Adams, et al. ("Adams")

Claims 24 and 25 are rejected as allegedly being obvious over Williams, in view of Adams (U.S. Patent No. 5,378,620). Williams is described above. Adams is cited for

disclosing rifampicin as an antibiotic that inhibits RNA polymerase in bacteria, *i.e.*, *E. coli*, that exhibits LEU-2 expressing plasmid. Applicant respectfully traverses.

In the first Office Action response, Applicant differentiated the instant invention from the combination of Williams and Adams. The point of differentiation is that the combination does not teach or suggest the determination of the relative locations of two or more atoms in a selected macromolecule in an intact biological compartment through using multidimensional NMR methods. The Examiner noted that this differentiating feature is not reflected in the rejected claims.

Therefore, Applicant has amended independent claim 1, and thus its dependent claims 24 and 25, in order to define structural information as "a representation of a first conformation of said selected macromolecule at a resolution sufficient to determine the relative locations of two or more atoms". Support for this amendment is found in the specification on page 9, lines 30-32. Applicant has also amended claim 1 in order to define the NMR data set as a "multidimensional" NMR data set. Support for this amendment is found in the specification in Examples 3 and 5-7.

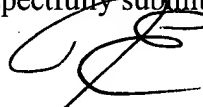
Since the combination of Williams and Adams does not disclose the determination of the relative locations of two or more atoms in a selected macromolecule in an intact biological compartment through using multidimensional NMR methods, the combination does not disclose each and every element of Applicant's invention. Accordingly, a *prima facie* case of obviousness can not be set forth. Therefore, claims 24 and 25 are in condition for allowance and Applicant respectfully requests withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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Attachment: Declaration of Volker Doetsch Under 37 C.F.R. § 1.132

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